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EXAMINER	
DEVI, SARVAMANGALA J N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/761,498	MICHON ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-65* is/are pending in the application.

4a) Of the above claim(s) *6,7,10,29-36,41-58 and 62-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8,9,11-28,37-40 and 59-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *050207*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Preliminary Amendments

1) Acknowledgment is made of Applicants' preliminary amendments filed 01/20/04, 01/26/07 and 03/17/07.

Election

2) Acknowledgment is made of Applicants' election filed 01/26/07 in response to the restriction and species election requirements mailed 09/26/06. Applicants have elected, with traverse, invention I, claims 1, 3-28, 37-40 and 59-61, and the *Streptococcus* Group B polysaccharide or oligosaccharide species; DTaP second immunogenic component species; and tetanus toxoid protein species.

With regard to the restriction requirement, Applicants' cite M.P.E.P § 803 and state that there are two criteria for a proper requirement for restriction between patentably distinct inventions: (a) The invention must be independent as claimed, and (b) There must be a serious burden if the restriction is not required. Applicants submit that all groups of the restricted claims are properly presented in the same application; undue diverse searching would not be required; and all claims should be examined together. Applicants allege that the Office has not shown that examination of all the pending claims would require undue searching and/or place a serious burden on the Office, which is a requisite showing for proper issuance of a restriction requirement. Applicants state that, of the five groups of invention identified, three are in the same class 424, and that to search prior art in a single class cannot be deemed undue diverse searching. Applicants assert that at a minimum, inventions I, III and V should also be examined together.

With regard to the species election requirement, Applicants' traversal is on the grounds that: (a) Applicants are entitled to prosecution of claims covering a reasonable number of species disclosed in an application in accordance with 37 C.F.R § 1.46; and (b) there would be no undue burden on the Office to conduct a substantive examination of the claims as related to the embodiments disclosed in the instant application. Applicants state that the election of species requirement is improper and that the Office may require an election of species to not more than a reasonable number of species before taking further action in the application. Applicants further submit that according to M.P.E.P § 806.04, an allowable generic claim may link a reasonable

number of species embraced thereby. Applicants' allege that the Office's position that 'one' is the maximum reasonable number of species is inconsistent with 37 C.F.R § 1.146 and the M.P.E.P. Applicants contend that the instant claims present a reasonable number of species embraced thereby and therefore are entitled to examination of all of the pending claims.

Applicants' arguments have been carefully considered, but are not persuasive for the following reasons. Contrary to Applicants' assertion, the Office has met the two criteria set forth in M.P.E.P § 803 for a proper requirement for restriction between patentably distinct inventions: (a) independent invention as claimed, and (b) a serious burden if the restriction is not required. The Office has shown that undue diverse and non-coextensive searching would be required since the methods of inventions II, III and V differ from one another in the distinct product or reagent(s) used therein, methods steps and parameters, method objectives, and ultimate goals used. The products used in these methods are divergent with regard to their structure and/or function, and classes/subclasses, each requiring separate and non-coextensive searches. The method of making a conjugate is unrelated to the method of immunizing a mammal, and the method of passive immunization. Therefore, searching the above-identified inventions together would not be coextensive and impose a serious search burden. The Office has established that inventions I and IV are drawn to two distinct products: (a) polysaccharide- or oligosaccharide-protein conjugate; and (b) an immunoglobulin or antigen binding fragment. As set forth previously, a polysaccharide is a carbohydrate composed of saccharide repeat units whereas antibodies are glycoproteins which include IgG that comprises 2 heavy and 2 light chains containing constant and variable regions, including framework regions which act as a scaffold for the 6 complementarity determining regions (CDRs) that function to bind an epitope. The two products are distinct molecules divergent with regard to their composition, structure, and function, each requiring a separate and non-coextensive search. Searching inventions I and IV together would impose a search burden. In addition, there is also non-patent literature search burden and examination burden. With regard to inventions I and II, and inventions I and III that are related as product and process of making or using the product, Applicants should note that as set forth in paragraphs 14 and 15 of the Office Action mailed 09/26/06, where Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or that otherwise include all the

limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. In the instant application, the claims belonging to inventions II and III would be retained as pending withdrawn claims. For the reasons delineated above, the restriction requirement set forth in the instant application is maintained and is hereby made FINAL.

Status of Claims

3) Claim 2 has been canceled via the amendment filed 01/20/04.

Claims 1, 3-27, 33-40, 43, 51-53, 55 and 58 have been amended via the amendment filed 01/20/04.

New claims 59-65 have been added via the amendment filed 01/20/04.

Claims 31, 38 and 59 have been amended via the amendment filed 01/26/07.

Claims 1 and 3-65 are pending.

Claims 6, 7, 10, 29-36, 41-58 and 62-65 have been withdrawn from consideration as being directed to a non-elected invention and species. See 37 C.F.R 1.142(b) and M.P.E.P § 821.03.

Claims 1, 3-5, 8, 9, 11-28, 37-40 and 59-61 are under examination. A First Action on the Merits is issued for these claims.

Information Disclosure Statements

4) Acknowledgment is made of Applicants' information disclosure statements filed 05/02/07. The information referred to therein has been considered and a signed copy is attached to this Office Action.

Priority

5) The instant application is a continuation of application SN 09/376,911, filed 08/18/1999, *now abandoned*, which claims priority to the provisional application, 60/097,120, filed 08/19/1998.

Specification

6) The instant specification is objected to for the following reasons:

(a) The first paragraph of the specification as amended via the amendment filed 01/20/04 does not accurately reflect current status of the prior non-provisional application as indicated above in italicized letters under the section 'Priority'.

(b) The use of the trademark in the instant specification has been noted. For example, see 'Superdex' on pages 18 and 21; 'Zwittergent 3-4' in paragraph bridging pages 20 and 21; and

'Tween 20' in Example 2. The recitation should be capitalized wherever it appears. See M.P.E.P 608.01(V) and Appendix I. Although the use of trademarks is permissible in patent applications, the propriety nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. It is suggested that Applicants examine the whole specification to make similar corrections to trademark recitations, wherever such recitations appear.

(c) 37 CFR 1.75(d)(1) provides, in part, that 'the terms and phrases used in the claims must find clear support or antecedent basis in the description so that the meaning of the terms in the claims may be ascertainable by reference to the description.'

Claims include the limitation 'N-propionated polysaccharide' or 'N-propionated oligosaccharide', which lacks clear support or antecedent basis in the specification.

(d) The instant specification uses certain abbreviated terminologies that are not understood. For example, 'DCC' in line 1 on page 9. Clarification/correction is requested.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

7) Claims 1, 16, 59, 60 and those dependent therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 1, as amended, includes the new limitations: 'coupled to a protein through β-position sites of one or more propionate moieties of the N-propionated polysaccharide or N-propionated oligosaccharide; wherein the N-propionated polysaccharide or N-propionated oligosaccharide directly coupled to the protein elicits protective antibodies reactive with the N-propionated polysaccharide or N-propionated oligosaccharide; wherein the N-propionated polysaccharide or N-propionated oligosaccharide is de-N-acetylated and N-acryloylated; wherein at least 50% of the N-propionated polysaccharide or oligosaccharide is de-N-acetylated; and wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues'. Claim 16, as amended, includes the new limitations: 'comprising an N-propionated polysaccharide or N-propionated oligosaccharide directly coupled to a protein through β-position sites of one or more propionate moieties of the N-propionated polysaccharide or N-propionated oligosaccharide;

wherein the conjugate elicits protective antibodies reactive with the N-propionated polysaccharide or N-propionated oligosaccharide .... wherein at least 50% of the N-propionated polysaccharide or N-propionated oligosaccharide is de-N-acetylated ..... coupling through β-position sites of one or more propionate moieties ...'. The conjugate of claim 5 comprising the N-propionated polysaccharide or the N-propionated oligosaccharide of GBS type Ia, type Ib, type II, type III, type V, type VIII, or combinations thereof is required to elicit 'protective antibodies reactive with the N-propionated polysaccharide or the N-propionated oligosaccharide of type Ia, type Ib, type II, type III, type V, type VIII, or combinations thereof. New claims 59 and 60, which depend from claims 1 and 16 respectively, include the limitations: 'wherein the de-N-acetylated polysaccharide or de-N-acetylated oligosaccharide is at least 95% N-acryloylated'. However, there is no support in these parts of the specification for a polysaccharide- or oligosaccharide-protein conjugate as claimed, comprising an N-propionated polysaccharide or N-propionated oligosaccharide, or an N-propionated polysaccharide or an N-propionated oligosaccharide of GBS type Ia, type Ib, type II, type III, type V, type VIII, or combinations thereof directly coupled to a protein through 'β-position sites of one or more propionate moieties' of the N-propionated polysaccharide or N-propionated oligosaccharide, having at least 50% the N-propionated polysaccharide or N-propionated oligosaccharide de-N-acetylated or having at least 95% of the N-acryloylated polysaccharide or oligosaccharide, wherein the conjugate elicits 'protective' antibodies reactive with the N-propionated polysaccharide or the N-propionated oligosaccharide. Applicants do not point to specific parts of the specification that provide descriptive support for the new limitations. No part of the original claims and the originally filed specification describe 'protective antibodies reactive with' any N-propionated bacterial or non-bacterial polysaccharide or oligosaccharide being elicited by the claimed conjugate. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any

amendments made to the disclosure. See MPEP 714.02 and 2163.06.

8) Claim 37 and those that depend therefrom are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 37, as amended, includes the limitations: 'protective immunity against at least one member of a genus of an organism from which the polysaccharide or oligosaccharide component of the polysaccharide-protein conjugate or oligosaccharide-protein conjugate was obtained'. However, there appears to be no descriptive support in the specification, as originally filed, for these added limitations. Applicants do not point to specific parts of the specification that provide descriptive support for the new limitations. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicants are invited to point to specific line and page numbers of the specification, as originally filed, that provide descriptive support for the limitations identified above, or alternatively, remove the new matter from the claim. Applicants should specifically point out the support for any amendment made to the disclosure. See MPEP 714.02 and 2163.06.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Scope of Enablement)

9) Claims 18 and 20 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate, a type II or type III GBS conjugate for example, wherein the coupling process is conducted at a pH of 9.5 in a carbonate/bicarbonate buffer, does not reasonably provide enablement for such a conjugate wherein the coupling is conducted at a pH of 7.0 and in a phosphate buffer, wherein the conjugate 'elicits protective antibodies' reactive with the N-propionated polysaccharide or N-propionated oligosaccharide, as claimed currently. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the Wands factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate comprising an N-propionated polysaccharide or N-propionated oligosaccharide directly coupled to a protein through beta-position sites of one or more propionate moieties of the N-propionated polysaccharide or N-propionated oligosaccharide, wherein the conjugate elicits protective antibodies reactive with the N-propionated polysaccharide or N-propionated oligosaccharide, wherein at least 50% of the N-propionated polysaccharide or N-propionated oligosaccharide is de-N-acetylated, and wherein the conjugate is produced by a method comprising direct coupling through beta-position sites of one or more propionate moieties of the N-propionated polysaccharide or the N-propionated oligosaccharide to a bacterial protein or a synthetic protein containing lysine or cysteine residues, wherein the coupling is conducted at a pH of about 7.0 in a phosphate buffer reagent. Thus, the claimed conjugate is required to 'elicit protective antibodies reactive with the N-propionated polysaccharide or N-propionated oligosaccharide'. The limitation 'coupling' is not limited to covalent coupling, but encompasses non-covalent coupling as well. The specification on page 10, lines 17-19 and 25-27 states that the conjugation is conducted at a neutral pH of about 7.0 and in a phosphate buffered reagent. However, this statement is not commensurate in scope with the evidentiary support within the instant specification. Instant Examples describe N-acryloylated polysaccharide- or oligosaccharide-protein conjugates wherein the conjugation was conducted by Michael addition at a pH of 9.5, or between about 9.0 and about 10.0 (see page 10) in a borate or carbonate/bicarbonate buffer. However, there is no showing that a bacterial or non-bacterial N-acryloylated polysaccharide or a bacterial or non-bacterial N-acryloylated oligosaccharide, including an N-acryloylated GBS polysaccharide or oligosaccharide, is successfully conjugated to a protein by Michael addition at a

pH of 'about 7.0' or in a phosphate buffer reagent such that the resulting conjugate 'elicits protective antibodies with the N-propionated polysaccharide or N-propionated oligosaccharide'. This is important because there is no certainty or predictability that this type of conjugation could optimally and/or effectively be conducted at a non-alkaline pH. The state of the art at the time of the invention indicated that conjugation by Michael addition is carried out in the alkaline range, i.e., above 9.0 in an appropriate buffer, such as, borate or carbonate buffer. For instance, Romanowska *et al.* (*Methods in Enzymol.* 242: 90-101, 1994 - Applicants' IDS) used a pH of 8.5, 9.5 and 10.5 for this type of conjugation (see page 94) and found a pH of 10.0 or 10.5 to be the optimal pH for coupling, which pH prevented protein degradation (see page 101). Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 1709-1711, 1990 - Applicants' IDS) taught that N-acryloylated oligosaccharide can be covalently conjugated to a protein by Michael reaction at a pH **greater** than 8.0 to 8.5 and at a pH of 10.5 (see page 1710). Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991) taught that even at a pH of 8.0 or 9.0 in phosphate buffer, the Michael reaction did **not** furnish appreciable conjugation; the reaction however proceeded smoothly at these two pH values in carbonate buffer. Roy *et al.* (*J. Chem. Soc., Chem. Commun.* 536-538, 1991 - Applicants' IDS) also taught that a very small amount of carbohydrate was conjugated in borate buffer at pH 8.0 (see paragraph bridging pages 537 and 538). Pon (*The Study of Polysialic acid Conjugates.* Master's Thesis, University of Ottawa, pp. 1-251, UMI Dissertation Services, 1992 - Applicants' IDS) taught that phosphate buffers at various pH values did not prove satisfactory during the conjugation process (see page 147, lines 2-4). With this teaching documented in the state of the art at the time of the invention and with the lack of evidence within the instant specification, it is not predictable that one of skill in the art would be able to produce the claimed conjugate that 'elicits protective antibodies reactive with the N-propionated polysaccharide or N-propionated oligosaccharide'. This is critically important because predictability or unpredictability is one of the *Wands* factors for enablement. In order for a conjugate to be protective, the process of conjugation has to take place effectively under conditions that are accepted in the art to be satisfactory, or under conditions that are shown within the instant specification or in the state of the art to be satisfactory such that the protective epitopes of the polysaccharide, oligosaccharide and/or the protein are retained and the conjugate elicits protective antibodies reactive with the polysaccharide or the oligosaccharide as claimed. Assuming

that the Michael reaction does take place to some extent at pH 7.0, it is unlikely that the resultant poorly conjugated polysaccharide or poorly conjugated oligosaccharide would elicit 'protective antibodies'. The instant specification does not demonstrate that the claimed conjugate synthesized at a coupling pH of about 7.0 would maintain the needed conformation and/or retain the necessary epitopes that elicit 'protective antibodies' reactive with the N-propionated polysaccharide or the N-propionated oligosaccharide as claimed. Accordingly, undue experimentation would have been required by one of skill in the art at the time of the effective filing date of the instant application to reproducibly practice the invention as claimed, due to the lack of specific guidance and/or direction, the lack of enabling disclosure, the art-demonstrated unpredictability in obtaining an effective N-propionated oligosaccharide-protein conjugate when a coupling pH of 7.0 or a phosphate buffer reagent is used, the unpredictability with regard to successful conjugation by Michael addition taking place at a non-alkaline pH of 7.0 or in a phosphate buffer medium, the breadth of the claims, and the quantity of experimentation necessary. The claims are viewed as not meeting the scope of enablement provisions of 35 U.S.C § 112, first paragraph.

10) Claims 1, 3, 4-9, 11-28, 37-40 and 59-61 are rejected under 35 U.S.C § 112, first paragraph, because the specification, while being enabling for a conjugate comprising, for example, an N-acryloylated group B streptococcus type III (GBS III) polysaccharide directly conjugated at the beta position to tetanus toxoid (wherein the percent N-acryloylation of the polysaccharide is undisclosed), and a pharmaceutical composition the same, said composition capable of inducing a homologous type III polysaccharide-specific opsonophagocytic antibody response, does not reasonably provide enablement for such a conjugate or composition comprising N-acryloylated GBS III polysaccharide-TT or N-acryloylated GBS III oligosaccharide-TT, or GBS type Ia, Ib, II, V, or VIII polysaccharide- or oligosaccharide-protein carrier conjugate, or any N-acryloylated bacterial polysaccharide or N- acryloylated oligosaccharide similarly conjugated to a TT or non-TT protein carrier and capable of providing 'protective antibodies' reactive with the N-propionated polysaccharide or the N-propionated oligosaccharide of a non-homologous strain or type of GBS III, or any other bacteria or organism from which the polysaccharide- or oligosaccharide component of the conjugate was obtained, as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make and/or use the invention commensurate in scope with these claims.

Instant claims are evaluated based on the Wands factors. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art; and
- The breadth of the claims.

In the instant case, claims 1 and 16 broadly encompass a conjugate that 'elicits protective antibodies reactive with the N-propionated polysaccharide or the N-propionated oligosaccharide', i.e., protective antibodies against any disease or condition including Group B streptococcal infection, cancer, yeast infections etc. A myriad of pathogenic organisms including pathogenic bacteria, and any number of serogroups, serotypes, or species of *Streptococcus,* and any types of Group B *Streptococci* are encompassed within the scope of the claims against which the claimed polysaccharide- or oligosaccharide-protein conjugate vaccine is required to elicit 'protective antibodies' to. Claims 37-40 depend directly or indirectly from claim 1 or 16. The limitation 'Streptococcus' encompasses multiple species, such as, *Streptococcus pyogenes*, *Streptococcus mutans*, *Streptococcus faecalis, Streptococcus pneumoniae* etc. Both homologous and heterologous strains or types of Group B *Streptococci* are encompassed within the limitation 'at least one member of a genus of an organism from which the polysaccharide or oligosaccharide .... was obtained' and within the limitation '*Streptococcus*'. The terms 'polysaccharide' and 'oligosaccharide' encompass lipopolysaccharide, capsular polysaccharide, a cell wall polysaccharide, exopolysaccharide etc. The protective ability of a lipopolysaccharide, cell wall polysaccharide, capsular polysaccharide, or exopolysaccharide of at least one member of a genus of an organism from which the polysaccharide or oligosaccharide .... was obtained', or the protective ability of a cell wall polysaccharide, capsular polysaccharide, or exopolysaccharide of any strain, serogroup, serotype, or type of *Streptococcus,* in a conjugate form is not predictable. The data provided for a *Streptococcus* in Table 6 are limited to a showing that the N-acryloylated group B *Streptococcus* type III capsular polysaccharide conjugated to tetanus toxoid by Michael

addition, on administration along with alum to laboratory animals, elicited homologous GBS type III capsular polysaccharide-specific opsonophagocytic antibody response as measured on day 52 post immunization. Table 6 or other parts of the specification do not disclose the percent N-acryloylation of the GBS-III polysaccharide contained in the GBS III-TT conjugate. There is no evidence that this conjugate would induce anti-capsular polysaccharide opsonophagocytic antibodies that would protect against any other strains, serogroups, serotypes, or types of '*Streptococcus*' other than the homologous strain of group B *Streptococcus* type III. This is important because, by and large, the opsonophagocytic GBS anti-capsular polysaccharide antibodies induced by a conjugate vaccine comprising the corresponding polysaccharide or oligosaccharide are strain- or type-specific. Similarly, an *E. coli* O111 O-specific oligosaccharide conjugate would not be expected to elicit protective antibodies against another strain or O-type of the same bacterium, for example *E. coli* serotype O157. From what is known in the art about the polysaccharide-specific opsonophagocytic response against a particular bacterial pathogen, or a particular serogroup, serotype, or capsular type of a particular bacterial pathogen, it is unlikely that a GBS III capsular polysaccharide-TT conjugate produced according to the instant invention would induce antibodies that are opsonophagocytic against heterologous *Streptococci*, for example, Group C streptococci, or heterologous type Ia, Ib, II, V, VIII, or a combination thereof. Neither there is evidence, nor is it predictable that a non-capsular polysaccharide, for example, of GBS III when conjugated as described in the instant application, would elicit 'protective antibodies' to *Streptococci* of heterologous capsular types, absent a concrete showing. Therefore, considerable amount of undue experimentation would have been required by one of skill in the art at the time the invention was made to practice the full scope of the invention due to the lack of evidence/guidance within the instant specification, the lack of working examples enabling the full scope of the claimed invention, the unpredictability factor, the breadth of the claims, and the quantity of experimentation necessary.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (Lack of Enablement)

11) Claims 25 and 40 are rejected under 35 U.S.C § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are evaluated based on the *Wands* analysis. Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

- The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;
- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the nature of the invention is related to a combination vaccine or a combination pharmaceutical composition comprising: (a) a pharmaceutically acceptable carrier; (b) a polysaccharide-protein conjugate or an oligosaccharide-protein conjugate comprising an N-propionated polysaccharide or N-propionated oligosaccharide directly linked to a protein through beta-position sites of one or more propionate moieties of the N-propionated polysaccharide or the N-propionated oligosaccharide, wherein the N-propionated polysaccharide or the N-propionated oligosaccharide directly coupled to the protein elicits 'protective antibodies' reactive with the N-propionated polysaccharide or the N-propionated oligosaccharide, wherein the N-propionated polysaccharide or the N-propionated oligosaccharide is de-N-acetylated and N-acryloylated and at least 50% of the N-propionated polysaccharide or the N-propionated oligosaccharide is de-N-acetylated, and wherein the protein is a bacterial protein or a synthetic protein containing lysine or cysteine residues; and (c) a second immunogen component selected from the group consisting of DTP, DTaP, tetanus-diphtheria, DTaP-Hib, DtaP-IPV-Hib, and combinations thereof. The elected polysaccharide or oligosaccharide is the *Streptococcus* Group B polysaccharide or oligosaccharide species; DTaP second immunogenic component species; and tetanus toxoid protein species. This means that the claimed vaccine or composition comprising the N-propionated *Streptococcus* Group B polysaccharide or oligosaccharide conjugated to tetanus toxoid wherein at least 50% of the N-propionated *Streptococcus* Group B polysaccharide or oligosaccharide is de-N-acetylated and further comprising the DTaP second immunogenic component or a combination second immunogenic component that comprises the DTaP is *required* to elicit 'protective antibodies' reactive with the N-propionated *Streptococcus* Group B polysaccharide or the N-propionated

Streptococcus Group B oligosaccharide. However, there is a lack of showing that an N-propionated *Streptococcus* Group B polysaccharide- or oligosaccharide-tetanus toxoid conjugate of the instant invention can successively be combined with a second component, such as, DTaP, or DTP, Td, DTap-Hib, DTaP-IPV-Hib, or combinations thereof. There is no showing that the instantly claimed conjugate when combined with one or more of any of the recited second component or combinations thereof, would retain its immunogenic function as a vaccine and would effectively elicit an optimal GBS polysaccharide- or GBS oligosaccharide-specific immune response, let alone an N-propionated GBS polysaccharide- or an N-propionated GBS oligosaccharide-specific 'protective' antibodies. This is important because the state of the art on combination vaccines at the time of the invention indicated the occurrence of potential interference by one or more added vaccine components. For instance, Barington *et al.* (*Infect. Immun.* 61: 432-438, 1993 – Applicants' IDS) taught that immunizations of conjugated polysaccharides and unconjugated (free) carrier protein (for example, TT in the instant case), lead to a non-epitope specific suppression of the antibody response not only to the carrier protein, but the polysaccharide as well. Corbel (*Biologicals* 22: 353-360, 1994 – Applicants' IDS) taught that the use of diphtheria and tetanus proteins as carriers for multiple polysaccharide conjugates may lead to epitope suppression of anti-polysaccharide responses (see abstract). Most importantly, the combining of DTaP and IPV or DTaP and IPV with a bacterial capsular polysaccharide-protein conjugate has been shown in the art to result in interference and a significant and pronounced reduction in immune response to IPV. For example, see page 1688 of Eskola *et al.* (*Lancet* 348: 1688-1692, 1996), who concluded that '[t]he immunogenicity of all antigens must be tested before new combinations can be accepted for vaccination programmes …'. In the instant case, it is neither shown within the instant specification, nor is it predictable that the instantly claimed GBS conjugate when combined with a preparation containing DTaP or Hib conjugate, i.e., DTap-Hib or DTaP-IPV-Hib, or a combination thereof, would not result in an immune response-suppressing effect on one or more vaccine components. Corbel further taught that the formulation of the combinations may present specific problems resulting from the interaction of the various components with each other and with the adjuvants and excipients (see page 353). Given the lack of evidence/guidance, the teachings in the state of the art on the potential interference by one or more added vaccine components and the suppression of antibody response to the polysaccharide or the carrier protein, the unpredictability factor, the

breadth of the claims, the lack of working examples, and the quantity of experimentation necessary, undue experimentation would have been required by one of ordinary skill in the art to practice the invention as claimed.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

12) The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his/her invention.

13) Claims 1, 3-5, 8, 9, 11-28, 37-40 and 59-61 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claims 1, 14 and 16 lack proper antecedent basis for the limitation: 'N-propionated oligosaccharide'. See lines 4-9 of claim 1; line 2 of claim 14; and lines 4, 6 and 10 of claim 16. For proper antecedence and to be consistent with the claim language used in lines 14 and 15 of claim 16, it is suggested that Applicants replace the above-identified limitation with the limitation --the N-propionated oligosaccharide--.

(b) Claims 1, 3-5, 11, 12, 15, 17 and 37 lack proper antecedent basis for the recitation: 'oligosaccharide'. See line 9 of claim 1; and line 2 of claims 3-5, 11, 12, 15 and 17; and lines 3 and 4 of claim 37.

(c) Claims 37 and 40 lack proper antecedent basis in the limitation: 'oligosaccharide-protein conjugate'. See line 4 of claim 37 and line 3 of claim 40.

(d) Claims 25 and 40 are incorrect in identifying 'Hib' as '*Haemophilus influenzae* type B'. The art identifies 'Hib' as --*Haemophilus influenzae* type b--. See title and 'Summary' of Eskola *et al.* (*Lancet* 348: 1688-1692, 1996).

(e) Claims 1 and 16, as amended, include the limitation: 'elicits protective antibodies reactive against the N-propionated polysaccharide or N-propionated oligosaccharide'. While it appears that the reactivity of the antibodies elicited by the claimed conjugate is 'with' N-propionated polysaccharide or N-propionated oligosaccharide, it is still unclear what these N-propionated polysaccharide- or N-propionated oligosaccharide-reactive antibodies are protective against. The need for protection 'against' an isolated or non-isolated N-propionated polysaccharide

or N-propionated oligosaccharide is not understood. It should be noted that the source or origin of the polysaccharide or oligosaccharide is undisclosed in the instant claims and therefore broadly encompasses a polysaccharide or oligosaccharide from any source, including nature, environment, a plant, an animal, or self antigens. Even if one assumed that the protectivity is against bacteria or a host cell from which the polysaccharide or oligosaccharide is obtained from, since the polysaccharide or oligosaccharide on the bacterium or a host cell from which these are obtained is present on their surface in native or unmodified form, i.e., non-N-propionated form, it is not clear how N-propionated polysaccharide- or N-propionated oligosaccharide-reactive antibodies can be 'protective against' bacteria or host cells that possess the native non-N-propionated polysaccharide. For example, if one used an N-propionated plant polysaccharide or N-propionated plant oligosaccharide in the claimed conjugate, it is not clear what would the resultant antibodies be protective against. Clarification/correction is requested.

(f) Claims 26 and 27 are indefinite and/or improperly broadening in scope in the limitation: 'an N-propionated polysaccharide-specific' or 'an N-propionated oligosaccharide-specific' immune response or immunoglobulin. Claims 26 and 27 depend from claims 1 and 16 respectively, which already recite an N-propionated polysaccharide or an N-propionated oligosaccharide. Does it mean that 'an N-propionated polysaccharide-....' or 'an N-propionated oligosaccharide-...' that is recited in the dependent claims 26 and 27 is different from the one recited in the base claim?

(g) Claim 16 is vague, indefinite and internally inconsistent in scope in the limitations: 'a protein' (see line 3) and 'a bacterial protein or a synthetic protein' (see part C). The former is broader in scope than the latter.

(h) Claim 26 is indefinite because it has improper antecedent basis in the limitation 'the conjugates according to any one of claim 1 and claim 16' [Emphasis added]. Claim 26 depends from claim 1 or claim 16, which is drawn to a 'conjugate', but not to 'conjugates'.

(i) Claims 3-5, 8, 9, 11-15, 17-28, 37-40 and 59-61, which depend directly or indirectly from claim 1 or 16, are also rejected as being indefinite, because of the vagueness or indefiniteness identified above in the base claim.

Objection(s)

14) Claims 1 and 16 are objected to for the use of the limitation ';' in lines 7 and 9 of claim 1 and line 4 of claim 16. It is suggested that Applicants replace it with a comma.

Relevant Prior Art

15) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Auzanneau *et al.* (*Bioorg. Med. Chem.* 4(11): 2003-2010, November 1996 - Applicants' IDS) taught conjugation of N-acryloylated penta- or hexa saccharide of Group A streptococcal cell wall polysaccharide conjugated to BSA or ovalbumin via the conjugate addition of the epsilon-amino groups of lysines on the proteins to produce soluble conjugates. The use of the conjugates as immunizing agents is taught. See abstract; 'Experimental' section; and Results and Discussion.

- Jennings *et al.* (WO 96/40239 - Applicants' IDS) disclosed an *N*-acyl modified group B meningococcal polysaccharide, for example, *N*-acryloylated group B meningococcal polysaccharide (GBMP) conjugated to a protein carrier, such as, tetanus toxoid, diphtheria toxoid, CRM197 and meningococcal outer membrane protein. The GBMP was first *N*-deacetylated and then treated with acryloyl chloride at a pH of 8.5 and then conjugated to tetanus toxoid. The conjugate is purified and equilibrated in PBS (i.e., a pharmaceutically acceptable carrier). The conjugate was used to immunize mice with or without adjuvants, such as, alum or stearyl tyrosine, wherein the conjugate induced group B meningococcal bactericidal antibodies (see Examples 1-4 and 7; page 8, lines 19-23; Tables 1-3; and page 10). The *N*-acryloyl GBMP-tetanus toxoid conjugate, its use in immunizing mice with or without alum, and its ability to induce anti-group B meningococcal bactericidal and protective antibodies that are significantly less cross-reactive with the native GBMP, are described in Example 7 and Tables 1-3.

- Roy *et al.* (*J. Chem. Soc. Chem. Commun.* 536-538, 1991 - Applicants' IDS) taught that the use of N-acryloylated precursors has distinct advantages over previous methodologies since, as originally proposed, these conjugated precursors offer two synthetic possibilities. It is taught that they can be efficiently polymerized with acryloyl-type monomers and secondly, amine groups of

proteins or of functionalized polymers can be used as nucleophiles to give glycoconjugates by Michael addition (see page 537, right column).

- Roy *et al.* (*Glycoconjugate J.* 7: 3-12, 1990 - Applicants' IDS) taught the production or synthesis of a poly-alpha(2-8)-*N*-acryloylneuraminic acid or an *N*-acryloylated sialic acid derivative (see pages 5-7; and Figure 2). It is taught that protein conjugates of the derivative have been prepared (see page 10). The colominic acid is first de-*N*-acetylated and then *N*-acylated or *N*-acryloylated using acryloyl chloride (see pages 4-7).

- Baumann *et al.* (*Biochemistry* 32: 4007-4013, 1993, Applicants' IDS) teach an N-acryloylated alpha (2->8) polysialic acid synthesized by de-N-acetylating the polysaccharide and treating the de-N-acetylated polysaccharide with acryloyl chloride as taught by Roy and Pon (1990). See paragraph bridging pages 4007 and 4008. Baumann *et al.* further teach producing alpha (2->8) polysialic acid conjugates by 'direct coupling' with the epsilon-aminolysine residues of a protein such as TT monomer. See page 4008, left column.

Remarks

16) Claims 1, 3-5, 8, 9, 11-28, 37-40 and 59-61 stand rejected.

17) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Central Fax number, (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

18) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

May, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER